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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/991,548	11/20/2001	Lennart Olsson	213542000101	4181

23308 7590 05/19/2005

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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 05/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/991,548	OLSSON ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49-59* is/are pending in the application.

4a) Of the above claim(s) *52,54,56,58 and 59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49-51,53,55 and 57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 3/2/05 is acknowledged and has been entered.

2. Applicant is reminded of Applicant's election with traverse of the invention of Group I (a method of modulating the activity of a cell surface receptor comprising a contacting step in the absence of exogenous ligand and wherein the level of receptor activation is increased) and the species erythropoietin receptor (EPOR) as the species of cell surface receptor and oligopeptide SEQ ID NO: 11 as the exogenous compound in Applicant's response filed 9/24/03, and erythropoietin (EPO) as the species of exogenous ligand in an interview with Mr. Ted Apple on 2/27/04 (Form PTOL-413 of record).

Newly added claim 52 is drawn to a method wherein contacting is done in the presence of a ligand which normally activates said receptor, i.e., in the presence of exogenous ligand), belongs to non-elected Group II.

Newly added claims 54 and 56 are drawn to a method wherein the level of receptor activation is decreased, i.e., they belong to non-elected Group III.

It is noted by the Examiner that newly added base claim 49 recites "said exogenous compound...has at least an amine, carbonyl, hydroxyl or carboxyl group, and comprising a cyclical carbon or heterocyclic structure". Thus the exogenous compound reads upon the elected peptide species SEQ ID NO: 11 because SEQ ID NO: 11 is a peptide that has at least a carboxyl group at the C-terminus, a hydroxyl group on the Tyr amino acid residue, a carbonyl group on the Val amino acid residues, an amine group on the Arg amino acid residues, and comprises a cyclical carbon structure that is a 6-carbon ring on the Tyr amino acid residue, and is a 23-mer with a molecular mass of 3,450 daltons, i.e., "less than about 2,500 daltons" recited in the said claims.

Claims 58 and 59 are drawn to a method wherein the exogenous compound "is characterized by being other than an oligopeptide" and claim 59 recites "wherein said exogenous compound comprises a heterocyclic aromatic structure", said heterocyclic aromatic structure not being present in the elected species SEQ ID NO: 11.

Accordingly, claims 52, 54 and 56 (non-elected Groups II and III) and claims 58-59 (non-elected species of Group I) are withdrawn from further consideration by the Examiner, 37 C.F.R. 1.142(b), as being drawn to non-elected inventions.

Claims 49-51, 53, 55 and 57 are being acted upon presently.

3. It is noted that this application appears to claim subject matter disclosed in prior copending Application No. 09/028,937, 08/788,820, 08/701,382 and 08/612,999, and the said copending applications are disclosed as being continuing applications in the first line of the specification. However, the three latter applications appear to be continuations-in-part. Applicant should amend the first line of the specification to update the relationship of the priority documents and to update the status of the 09/028,937 parent application.

Applicant's arguments in the amendment filed 3/2/05 (of record) have been fully considered, but are not persuasive.

It is the Examiner's position that there is disclosure in the instant application and in 09/028,937 for which there is no disclosure in the 08/788,820, 08/701,382 and 08/612,999 applications, for example, "activation sequence" and interleukin receptors IL-3 through IL-9, IL-11 through IL-15, and IL-17, TPO receptor, prolactin receptor, TCR, CNF receptor, granulocyte colony stimulating factor receptor. In addition, there is also disclosure in all subsequently listed applications that is not present in the original 08/612,999 application.

4. The disclosure is objected to because of the following informality:

In the brief description of the drawings for Figure 1, the disclosure (on page 5 at line 16) is "Figures 1A and 1B". However, the Figure 1 has a top and bottom panel that are not labeled A and B.

Appropriate correction is required.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 49-51, 53, 55 and 57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The amendatory material not present in the originally filed disclosure is as follows:

"said exogenous compound is characterized by being other than a MHC class 1 alpha-I domain sequence".

7. Claims 49-51, 53, 55 and 57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention of the claimed method of modulating the activity of a cell surface receptor.

The instant claims encompass a method of modulating (activating) the activity of a cell surface receptor, including of a type-2 cell surface receptor such as those recited in the instant claims, comprising contacting the said receptor with an exogenous compound that binds an activation sequence on the said receptor, wherein the activation sequence of the said receptor is a segment of the cell surface receptor having at least 10% amino acid sequence identity and has at least 35% sequence similarity with a sequence of the same length from an MHC Class I alpha-1 domain sequence, the said contacting being accomplished in the absence of any exogenous ligand. The instant claims encompass a method for modulating the activity of ***any type-2 cell surface receptor*** that has the recited sequence identity and similarity to any segment of the same length from an MHC Class I alpha-1 domain in the case of claims 49-51, 53 and 55, or a method for modulating the activity of the type-2 cell surface receptors recited in claim 57, comprising using ***any exogenous compound,*** including oligopeptides or small organic molecules, that binds to an activation sequence and produces the function of modulating (increasing) a non-specified activity (exclusive of instant claim 57) of a receptor. There is insufficient disclosure in the specification of a method using said exogenous compound.

The specification discloses (on page 13 at lines 13-16) that activation sequences or internalization sequences are involved in modulation of receptor responses. The specification further discloses (on page 15 at lines 23-27) that the activation sequences are initially identified by homology to the sequence of an alpha1-domain of an MHC Class I antigen and (on page 16 at the last 5 lines) that the amino acid sequence of the receptor region of interest, i.e., "the activation sequence" will have at least about 10% or at least about 15-20% sequence identity and at least about 30% or at least about 35%sequence similarity as determined by using the Wisconsin Package, version 8.0-open VMS, Genetics Computer Group. The specification discloses that MHC Class I antigens include human MHC class I antigens and mammalian equivalents thereof, such as Class I antigens of the H-2 locus of mice. The specification discloses examples (on pages 17-19) of peptides having at least about 35% sequence similarity with the

sequence of an alpha-1 domain (such as SEQ ID NO: 1 of the instant application which is a 23-mer) of an MHC Class I antigen. The specification further discloses (at the paragraph spanning pages 14 and 15) that the activation sequence is usually not directly involved in ligand binding and that an activation sequence from one receptor will not activate a different receptor. The specification discloses (at the paragraph spanning pages 27 and 28) that an exogenous compound can be any compound not produced endogenously by the cell or organism such as chemical and small organic moieties and the oligopeptides disclosed in the specification.

The specification discloses oligopeptides that have an amino acid sequence *corresponding to* the activation sequence of the extracellular domain of a cell surface receptor. SEQ ID NO: 2-35 are fully defined oligopeptide sequences that are disclosed in the instant specification that are subsequences of naturally occurring receptors (pages 18-19). The specification discloses that "corresponds" means either that the oligopeptide is identical to all or part of the activation sequence, or that the oligopeptide has substantial homology to the activation sequence and may have amino acid substitutions, deletions or insertions as compared to the activation sequence (page 20 at lines 5-9).

There is no recitation in the instant claims 49-51, 53, 55 and 57 of what the exogenous compound is, other than it is "other than a MHC Class I alpha-1 domain sequence" "that is from "more than 100 to less than about 2,500 daltons", "has at least an amine, carbonyl, hydroxyl or carboxyl group", and "comprising a cyclical carbon or heterocyclic structure", i.e., being other than a MHC class I alpha-1 domain sequence encompasses any sequence that is a peptide that is less than about 2,500 daltons (i.e., is a rough approximate length limitation for the peptide), that possesses at least one of the recited groups that are common to most or all peptides and that comprises an amino acid residue that has a cyclical carbon or heterocyclic structure, i.e., that contains for example, Tyr, Pro, Trp or His. In-other-words, the exogenous compound may be any compound of any type, if a peptide, it is of unknown sequence and of rough approximate upper length limit with some amino acid residues having the recited groups and with no correlation of structure to function; if a small organic compound, it is one of undisclosed structure and with approximate molecular weight and with no correlation of structure to function. There is no recitation of what that function is, except for claim 55.

The recitation of "exogenous compound" "other than a MHC Class I alpha-1 domain sequence" "that is from "more than 100 to less than about 2,500 daltons", "has at least an amine, carbonyl, hydroxyl or carboxyl group", and "comprising a cyclical carbon or heterocyclic structure" is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by the property of being exogenously added, having a rough upper length limitation if it is a peptide or of approximate molecular mass if it is not a peptide, and containing certain functional groups at unspecified positions that aid in hydrogen bonding and containing cyclical or heterocyclical structures of undisclosed composition and position in the exogenous

compound, and being capable of modulating activity of a cell surface receptor. It does not specifically define any of the compounds that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. For example, may peptides of about 20 amino acid residues in length and containing a tyrosine and having a C-terminal carboxyl group would not be expected to have the claimed function. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. In addition, a definition by function does not suffice to define the genus because it is only an indication of what the property the compound has, and if one extends the analysis in the instant case, what the compound does (i.e., it binds to an activation sequence on a cell surface receptor and modulates an undisclosed activity), rather than what it is. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06. It is only a definition of a useful result rather than a definition of what achieves that result. Many such species may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material.

One of skill in the art would not have recognized that Applicant was in possession of the necessary common attributes or features possessed by the members of the genus.

Applicant's arguments (of record on pages 7-10) in Applicant's amendment filed 3/2/05 have been fully considered but are not persuasive.

An Applicant may show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that the Applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. Enzo Biochem. 323 F.3d at 964, 63 USPQ2d at 1613.

It is the Examiner's position that the instant claims are drawn to a method of modulating some activity of a type 2 cell-surface receptor (in the case of claim 55, wherein the activity comprises a conformational change in the receptor sufficient to elicit a phosphorylation event) containing an activation sequence that is characterized as recited in the instant claims, said method encompassing both *in vitro* and *in vivo* modulation, using an exogenous compound that does not, in response to Applicant's assertion, have a cyclic structure and defined substituents as enunciated supra in the instant rejection, i.e., the method encompasses modulating a response using an exogenous compound where the structure of the compound is not described except as

not being an alpha-1 MHC class I domain sequence, having a molecular mass from more than 100 to less than about 2,500 daltons, and having some functional groups common to most if not all peptides and most small non-peptide molecules, said functional groups disclosed in the specification as being there to provide potential hydrogen bonding capability to the compound, and comprising some cyclical carbon or heterocyclical structure, again common to peptides and small non-peptide organic molecules, and wherein there is no disclosure as to what structure correlates with functional activity. The WO 04/05323 document cited by Applicant as describing compounds that were discovered following the teachings of the subject invention has not been provided to the Examiner, and it has not been considered. It is the Examiner's further position that the instant claims are not drawn to a method for finding a product, but rather to a method of using the product to modulate the activity of a receptor. Except for the SEQ ID NO: 2-35 disclosed in the instant specification that are subsequences of cell surface receptors that correspond to the activation sequences of the said receptors that they derive from, no specific structural and functional characteristics and structure/function relationships are disclosed for other exogenous compounds, including peptides. As to Applicant's arguments that they possess a pioneering invention and to "possession" in general, that compounds were discovered and disclosed in WO 04/05323 and that broad inventions should be claimed broadly, it is the Examiner's position that there is no force to an argument that the written description requirement was satisfied because the disclosure revealed a broad invention from which [later filed] claims carved out a patentable portion. In addition, a biomolecule sequence described only by a functional characteristic (and/or in this case to non-functionally related structural features common to sequences that are not predictably or at all associated with conferring the functional characteristic because they are present in sequences that don't possess the functional activity), without any known or disclosed correlation between that function and the structure of the sequence normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence. See MPEP 2163.

With regard to Applicant's arguments as to using glycine or leucine walks to identify essential amino acid residues for binding, if there is no disclosure of structure and structure vs functional relationship, there is no starting point for synthesizing a peptide, which according to the molecular mass limitation recited in the instant claims can be from approximately two amino acid residues up to about 65 amino acid residues (given that the molecular weight of the natural amino acid residues ranges from 75 daltons to 204 daltons). It follows that for a 20-mer peptide for instance, there are 20 positions, each of which may be occupied by one of 20 of the naturally occurring amino acid residues (and not considering the additional permutations implied by using non-naturally occurring amino acid residues) or 20^{20} possible peptides. It is the Examiner's position that the exogenous compound recited in the instant claims is not limited to SEQ ID NO: 2-35 or substitution variants of the said SEQ ID NO, or to peptides at all.

8. Claims 49-51, 53, 55 and 57 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 49-51, 53, 55 and 57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an ***in vitro*** method for modulating the activity of a type-2 receptor containing an activation sequence that is one of the disclosed receptors from which SEQ ID NO: 2-35 are obtained using an exogenous compound that is an oligopeptide that is one of SEQ ID NOS: 2-35, does not reasonably provide enablement for the claimed method of modulating activity of a receptor that comprises any activation sequence (and including wherein said activation sequence has at least 10% amino acid sequence identity and at least 35% sequence similarity with the sequence of an alpha1-domain sequence of an MHC Class I antigen), nor wherein the receptor is any receptor and the exogenous compound is any exogenous compound, such as chemical and small organic moieties and oligopeptides that are not one of SEQ ID NO: 2-35 or SEQ ID NO: 2-35 substitution variants with receptor modulating activity, nor wherein the method is an *in vivo* method using any exogenous compound. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification does not disclose how to make/and or use the exogenous compounds of the claimed method.

The specification has not enabled the breadth of the claimed invention in view of the teachings of the specification because the claims encompass any exogenous compound in the case of instant claims 49-51, 53, 55 and 57 and any type-2 receptor in the case of instant claims 49-51, 53 and 55, and also encompass *in vivo* methods of receptor modulation. There is no recitation in instant claims 49-51, 53, 55 and 57 of what the exogenous compound is, other than it is "other than a MHC Class I alpha-1 domain sequence" "that is from "more than 100 to less than about 2,500 daltons", "has at least an amine, carbonyl, hydroxyl or carboxyl group", and "comprising a cyclical carbon or heterocyclic structure", i.e., being other than a MHC class I alpha-1 domain sequence encompasses any sequence that is a peptide that is less than about 2,500 daltons (a rough approximate length limitation for the peptide), that possesses at least one of the recited groups that are common to most or all peptides and that comprises an amino acid residue that has a cyclical carbon or heterocyclic structure, i.e., that contains for example, Tyr, Pro, Trp or His. In-other-words, the exogenous compound may be any compound of any type, if a peptide, it is of unknown sequence and of rough approximate length limit with some amino acid residues having the recited groups and with no disclosure of correlation of structure to function; if a small organic compound, it is one of undisclosed structure of approximate molecular weight with no disclosure of

structure function relationship. There is no recitation of what that function is, except for claim 55.

The specification discloses (on page 13 at lines 13-16) that activation sequences or internalization sequences are involved in modulation of receptor responses. The specification further discloses (on page 15 at lines 23-27) that the activation sequences are initially identified by homology to the sequence of an alpha1-domain of an MHC Class I antigen and (on page 16 at the last 5 lines) that the amino acid sequence of the receptor region of interest, i.e., "the activation sequence" will have at least about 10% or at least about 15-20% sequence identity and at least about 30% or at least about 35%sequence similarity as determined by using the Wisconsin Package, version 8.0-open VMS, Genetics Computer Group. The specification discloses that MHC Class I antigens include human MHC class I antigens and mammalian equivalents thereof, such as Class I antigens of the H-2 locus of mice. The specification discloses examples (on pages 17-19) of peptides having at least about 35% sequence similarity with the sequence of an alpha-1 domain (such as SEQ ID NO: 1 of the instant application which is a 23-mer) of an MHC Class I antigen. The specification further discloses (at the paragraph spanning pages 14 and 15) that the activation sequence is usually not directly involved in ligand binding and that an activation sequence from one receptor will not activate a different receptor. The specification discloses (at the paragraph spanning pages 27 and 28) that an exogenous compound can be any compound not produced endogenously by the cell or organism such as chemical and small organic moieties and the oligopeptides disclosed in the specification.

The specification discloses oligopeptides that have an amino acid sequence *corresponding to* the activation sequence of the extracellular domain of a cell surface receptor. SEQ ID NO: 2-35 are fully defined oligopeptide sequences that are disclosed in the instant specification that are subsequences of naturally occurring receptors (pages 18-19). The specification discloses that "corresponds" means either that the oligopeptide is identical to all or part of the activation sequence, or that the oligopeptide has substantial homology to the activation sequence and may have amino acid substitutions, deletions or insertions as compared to the activation sequence (page 20 at lines 5-9).

There is no guidance in the specification as to what alterations result in a functional exogenous compound, including an oligopeptide, or which receptors contain an "activation sequence capable of binding an "exogenous compound", other than the oligopeptides SEQ ID NO: 2-35 and the receptors from which they are derived, respectively, and further there is no disclosure of working examples of *in vivo* modulation. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain functional activity, and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e., its activity) are not well understood and are therefore not predictable (Ngo et al. The Protein Folding Problem and Tertiary Structure Prediction,

Merz & LeGrand, Birkhauser Boston, pages 491-495, 1994, entire article, especially Section 6, paragraph 1, of record), it would require undue experimentation for one of skill in the art to arrive at other amino acid sequences that would have functional activity. In other words, since it would require undue experimentation to identify exogenous compounds, including amino acid sequences that have functional activity, it would require undue experimentation to make the corresponding sequences.

In addition, *in vivo* pharmaceutical therapies in the absence of *in vivo* clinical data are unpredictable for the following reasons; (1) the compound may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the compound; (2) the compound may not reach the target area because, i.e. the compound may not be able to cross the mucosa or the compound may be adsorbed by fluids, cells and tissues where the compound has no effect; and (3) other functional properties, known or unknown, may make the peptide or non-peptide compound unsuitable for *in vivo* therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

The enablement provided by the specification is not commensurate with the scope of the claims. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

Applicant's arguments (of record on pages 7-10) in Applicant's amendment filed 3/2/05 have been fully considered but are not persuasive.

It is the Examiner's position that the instant claims are drawn to a method of modulating some activity of a type 2 cell-surface receptor (in the case of claim 55, wherein the activity comprises a conformational change in the receptor sufficient to elicit a phosphorylation event) containing an activation sequence that is characterized as recited in the instant claims, said method encompassing both *in vitro* and *in vivo* modulation, using an exogenous compound that does not, in response to Applicant's assertion, have a cyclic structure and defined substituents as enunciated supra in the instant rejection, i.e., the method encompasses modulating a response using an exogenous compound where the structure of the compound is not described except as not being an alpha-1 MHC class I domain sequence, having a molecular mass from more than 100 to less than about 2,500 daltons, and having some functional groups common to most if not all peptides and most small non-peptide molecules, said functional groups disclosed in the specification as being there to provide potential hydrogen bonding capability to the compound, and comprising some cyclical carbon or heterocyclical structure, again common to peptides and small non-peptide organic molecules, and wherein there is no disclosure as to what structure correlates with functional activity. The biomolecule sequence is disclosed only by non-functionally related structural features common to sequences that are not predictably or at all associated with conferring the functional characteristic, and there is no disclosed correlation between that function and the structure of the sequence.

Except for the SEQ ID NO: 2-35 disclosed in the instant specification that are subsequences of cell surface receptors that correspond to the activation sequences of the said receptors that they derive from, no specific structural and functional characteristics and structure/function relationships are disclosed for other exogenous compounds, including peptides. With regard to Applicant's arguments to using glycine or leucine walks to identify essential amino acid residues for binding, it is the Examiner's position that the exogenous compound recited in the instant claims is not limited to SEQ ID NO: 2-35 or substitution variants of the said SEQ ID NO, or to peptides at all. If there is no disclosure of structure and structure vs functional relationship, there is no starting point for synthesizing a peptide, which according to the molecular mass limitation recited in the instant claims can be from approximately two amino acid residues up to about 65 amino acid residues (given that the molecular weight of the natural amino acid residues ranges from 75 daltons to 204 daltons). It follows that for a 20-mer peptide for instance, there are 20 positions, each of which may be occupied by one of 20 of the naturally occurring amino acid residues (and not considering the additional permutations implied by using non-naturally occurring amino acid residues) or 20^{20} possible peptides.

The WO 04/05323 document cited by Applicant as describing compounds that were discovered following the teachings of the subject invention has not been provided to the Examiner, and it has not been considered. As to Applicant's arguments that they possess a pioneering invention and that compounds were discovered and disclosed in WO 04/05323 that are suitable exogenous compounds and that broad inventions should be claimed broadly, it is the Examiner's position that the instant claims are not drawn to a method for finding a product, but rather to a method of using the product to modulate the activity of a receptor. An assay for finding a product is not equivalent to the recitation of a method of using a product that must be made.

9. The limitation "wherein said activation sequence is a segment of said cell surface receptor having at least 10% amino acid sequence identity and at least 35% sequence similarity..." do not have support in the parent application 08/612,999. Also, the limitations 'IL-3 through IL-17 receptors, GCS, TPO, prolactin, TCR and CNF receptors' recited in instant claim 57 do not have support in the parent applications 08/612,999, 08/701,382 and 08/788,820. The limitation "cell surface receptor containing an activation sequence" is only disclosed in parent application 09/027,937. (For example, in parent case serial no. 08/788,820 an "internalization sequence" is disclosed. Therefore, with regard to application of prior art, the instant application with regard to claims 49-51, 53 and 55 are only entitled to priority of the parent application 08/701,382, i.e., 8/22/1996, with regard to claim 57, that of parent application 09/027,937, i.e., 2/24/1998.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 49-51, 53, 55 and 57 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 95/05189 (IDS reference) as evidenced in the disclosure in the instant specification on page 26 at lines 17-28 and on pages 16 at lines 5-30 and page 17 at lines 1-2 and 22-23 and as evidenced by U.S. Patent No. 5,384,243 A.

WO 95/05189 teaches a method of modulating the internalization of a cell surface receptor, i.e., various cell surface receptors including type-1 and type-2 receptors (see entire document), containing an activation sequence, comprising binding an exogenous compound, i.e., various peptides that bind to a receptor and are comparable to polymorphic sequences in the alpha-2 domain of Class I, and wherein the cell is a human cell, the contacting is done in the absence of any exogenous ligand which normally activates the receptor, and wherein the level of receptor activation is increased and endocytosis, i.e., internalization, is decreased. WO 95/05189 teaches the EGF receptor, the transferrin receptor and the receptors for interleukins (1, 2, 3, 4) are receptors that are either internalized or recycled and are of particular interest for use in the method of the invention. WO 95/05189 teaches using peptides of various lengths, including for example, less than 10 amino acid residues or 20 amino acid residues, which meet the molecular weight limitation for the exogenous compound of the instant claims, said peptides having a carboxyl group at the carboxy terminus of the peptides and comprising a cyclical carbon since WO 95/05189 teaches including the sequence RYY at the end, the "Y" or Tyr residue comprises a cyclical carbon structure (especially page 6 at the last paragraph and continuing on to page 7 through line 21, page 10 at lines 17-29, pages 12-20, examples, table 4, claims).

The disclosure in the instant specification on page 26 at lines 17-28 and on page 16 at lines 5-30 and page 17 at lines 1-2 and 22-23 is that the EGF and transferrin receptors and those for IL-1, 2, 3 and 4 are type –2 receptors that have the claimed activation sequence.

Evidentiary reference U.S. Patent No. 5,384,243 A discloses that the EGF receptor mediates signal transduction by virtue of an intrinsic protein-tyrosine kinase activity, i.e., by phosphorylation (especially column 1 under "Background Information").

With respect to the limitation "wherein said activation comprises a conformational change in said receptor sufficient to elicit a phosphorylation event" recited in instant claim 55, the claimed process appears to be the same or similar to the process of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the process of the instant invention to those of the prior art, the burden is on applicant to show an unobvious distinction between the process of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Applicant's arguments (of record on page 11) in Applicant's amendment filed 3/2/05 have been fully considered but are not persuasive. Briefly the argument is that the reference believed that it was the MHC sequence that was active based upon the erroneous premise that the receptor when bound to its ligand would bind to an MHC molecule and be endocytosed, but that as evidenced by the subject invention, it is a second molecule of the receptor that binds, not an MHC molecule

It is the Examiner's position that the reference teaches binding an alpha-2 region peptide to a type-2 receptor, the teaching being that the precise mechanism whereby MHC class I antigens and agonistic or antagonistic agents modulate surface receptors is unknown, reference to interactions between MHC antigens, agents and receptors are intended to include direct binding between any of these molecules as well as indirect interactions (especially page 6), the "agent" being the endogenous compound of the instant claims. It is the Examiner's position that the art reference meets the claim limitations because it teaches a method of modulating the activity of a type-2 receptor using an alpha-2-region peptide to bind to the said receptor. In addition, Applicant's specification discloses that regulation of receptor internalization by the MHC class I molecule is shown by Olsson et al, and that peptides derived from the alpha 1 domain of the MHC class I protein inhibit internalization of some receptors, thereby increasing the steady-state number of active receptors on the cell surface, and that Stagsted et al demonstrate that such peptides inhibit the internalization of glucose transporters and insulin-like growth factor II receptors (paragraph spanning pages 3 and 4 of the instant specification).

12. Claims 49-51, 53, 55 and 57 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 95/05189 (IDS reference) as evidenced in the disclosure in the instant specification on page 26 at lines 17-28 and on pages 16 at lines 5-30 and page 17 at lines 1-2 and 22-23 and as evidenced by U.S. Patent No. 5,384,243 A.

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With respect to the limitation "wherein said activation comprises a conformational change in said receptor sufficient to elicit a phosphorylation event" recited in instant claim 55, the claimed process appears to be the same or similar to the process of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the process of the instant invention to those of the prior art, the burden is on applicant to show an unobvious distinction between the process of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

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13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 49-51, 53, 55 and 57 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 7 of copending Application No. 10/074,695. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of the 10/074,695 application comprising use of an oligopeptide comprising an internalization sequence recited in claim 7 of the 10/074,695 application is encompassed by the claimed method of the instant application, said method comprising use of an exogenous compound to modulate the activity of a cell surface receptor, because the oligopeptide recited in the 10/074,695 application is an oligopeptide corresponding to the extracellular domain of a cell surface receptor and the exogenous compound recited in the method of instant claims 49-51, 53, 55 and 57 reads on an oligopeptide that binds to an activation sequence on the extracellular domain of a cell surface receptor.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

15. Claims 49-51, 53, 55 and 57 are directed to an invention not patentably distinct from claim 7 of commonly assigned copending Application No. 10/074,695. Specifically, the method of the '695 application comprising use of an oligopeptide comprising an internalization sequence recited in claim 7 of the 10/074,695 application is encompassed by the claimed method of the instant application, said method comprising use of an exogenous compound to modulate the activity of a cell surface receptor, because the oligopeptide recited in the 10/074,695 application is an oligopeptide corresponding to the extracellular domain of a cell surface receptor, and the exogenous compound recited in the method of instant claims 49-51, 53, 55 and 57 reads on an oligopeptide that binds to an activation sequence on the extracellular domain of a cell surface receptor.

16. The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned Application No. 10/074,695, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 35 U.S.C. 103(c) and 37 CFR 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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May 6, 2005

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